§ 2.125(g) and these issues were not considered in this rulemaking.

(Comment 39) Prior to publication of the 2004 proposed rule, we received a comment from a manufacturer of MDI components submitted in response to the Stakeholders' petition. The manufacturer said it has the ongoing capacity to supply MDI components necessary for ongoing use of CFC MDIs, including albuterol CFC MDIs, and it will continue production as long as there is sufficient demand.

While we appreciate the information contained in this comment, the continued availability of MDI components necessary for continuing use of CFC MDIs is also not a criterion under § 2.125(g) upon which we may base our decision.

(Comment 40) One speaker at the PADAC meeting suggested that FDA monitor patient compliance and access to albuterol HFA MDIs and reserve the right to allow a certain number of albuterol CFC MDIs to be sold in case of a real emergency.

Under the Clean Air Act, a use of an ODS is either essential or it is ~~n~~ot. We are currently unaware of any interpretation of the provisions of the Clean Air Act that would give us the flexibility to allow emergency ~~use~~ sale or distribution of a CFC MDI once its use is determined to be non-essential.

(Comment 41) One comment recommended that we not set an effective date until we are certain that adequate production capacity will exist.

In choosing December 31, 2008, as the effective date of this rule, we did so with every reasonable expectation that adequate supplies and production capacity will exist by that time.

(Comment 42) A comment recommended that we not establish a date beyond which retail pharmacies are barred from selling albuterol CFC MDIs, even if we did establish a date beyond which albuterol CFC MDIs could not be manufactured.

The sale of remaining stocks of albuterol CFC MDIs was one of the factors we considered in establishing an effective date that is well after the date we expect the transition to HFA MDIs to be substantially completed by manufacturers of albuterol MDIs. This additional buffer period should give wholesalers and retailers adequate time to dispose of stocks of albuterol CFC MDIs. That being said, we do not have the authority to establish an effective dates for wholesalers and retailers that differs from an effective date for manufacturers. We can only make a determination on the date by which the criteria set out in § 2.125(g) will be met and the use of ODSs in albuterol MDIs is no longer essential. Once a product is no longer an essential use, the prohibitions in section 610 of the Clean Air

Act automatically come into play. However, section 610 of the Clean Air Act only applies to sales in interstate commerce. ~~EPA has informed us that retail pharmacies dispensing albuterol CFC MDIs to out-of-State patients for the time necessary to eliminate reasonable stocks of the MDIs after the effective date of this rule will not be a target of enforcement activity. The determination of what constitutes reasonable stocks could vary depending on the speed of the transition, and i~~If shipments of albuterol CFC MDIs by producers have stopped by December 31, 2007, or shortly thereafter, wholesalers and retailers should not find it difficult to distribute their stocks ~~it may be reasonable to expect that all wholesale and retail stocks will be distributed~~ by December 31, 2008.

G. CFCs and the Environment

(Comment 43) A few comments asserted that CFCs used in MDIs do not have an adverse impact on the environment because the CFCs are inhaled rather than being released into the environment.

Nearly all of the CFCs inhaled into the lungs from an MDI are almost immediately exhaled into the environment. The small amounts of CFCs absorbed into the body are later excreted and exhaled without being broken down. Essentially all of the CFCs released from an MDI end up in the atmosphere with resulting harm to the stratospheric ozone layer.

(Comment 44) A few comments asserted that the amount of ODSs released from albuterol CFC MDIs is insignificant, and eliminating their use would not provide any environmental benefit.

The United States evaluated the environmental effect of eliminating the use of all CFCs in an environmental impact statement (EIS) in the 1970s (see 43 FR 11301, March 17, 1978). As part of that evaluation, FDA concluded that the continued use of CFCs in medical products posed an unreasonable risk of long-term biological and climatic impacts (see Docket No. 96N-0057). In 1990, Congress enacted Title VI of the Clean Air Act, which codified the decision to fully phase out the use of CFCs over time. ~~We note that the environmental impact of individual uses of nonessential ODSs must not be evaluated independently, but rather must be evaluated in the context of the overall use of ODSs. Cumulative impacts can result from individually minor but collectively significant actions taking place over a period of time (40 CFR 1508.7). Significance cannot be avoided by breaking an action down into small components (40 CFR 1508.27(b)(7)). Although it may appear to some that the use of CFCs in albuterol MDIs is only a small part of total ODS use and therefore should be exempted, the elimination of CFCs in albuterol MDIs is only one of many steps that are part of the overall phaseout of ODS use. If each small step were provided~~

~~an exemption, the cumulative effect would be to prevent environmental improvements. In any case,~~ Congress did not assign us the task of determining what amount of environmental benefit would result from the removal of CFC-containing ~~"~~medical devices,~~"~~ diagnostic products, drugs, and drug delivery systems from the market. Congress did instruct us to determine whether such ~~"medical devices"~~products are essential. This rulemaking ~~merely~~ fulfills that obligation.

(Comment 45) A comment asserted that the Montreal Protocol is working well and that according to the Executive Summary of the "World Meteorological Organization Global Ozone and Research Project--Report No. 47: Scientific Assessment of Ozone Depletion: 2002" (Executive Summary) (available at http://www.unep.org/ozone/Publications/6v_science%20assess%20panel.asp), the continuing use of CFCs in albuterol MDIs would delay restoration of the Earth's ozone layer to its 1980 condition by an insignificant time past the currently projected date of 2050. The comment quoted the following passage from page xvii of the Executive Summary:

> The updated, best-estimate scenario for future halocarbon mixing ratios suggests that the atmospheric burden of halogens will return to the 1980 pre-Antarctic-ozone-hole levels around the middle of the 21st century, provided continued adherence to the

fully amended and adjusted Montreal Protocol. Only small improvements would arise from further reduced production allowances in the future.

The size of the delay in the date the ozone layer will be restored to its 1980 condition is not a criterion~~a~~ in determining which medical devices, diagnostic products, drugs, and drug delivery systems are essential under the Clean Air Act. These criteria are set out in § 2.125 and discussed above. However, we note that the estimate described in the quoted paragraph assumes "continued adherence to the fully amended and adjusted Montreal Protocol." As we discussed in section II.C.2 of this document, Decision IV/2 envisioned elimination of the production and importation of CFCs by January 1, 1996, by ~~part~~Parties that are developed countries. Although production and importation of CFCs for use in albuterol MDIs are permitted, year to year, as an essential use under the Montreal Protocol, we fail to see how a rule that permits ~~production~~ sale and distribution of albuterol CFC MDIs into 2008 can be characterized as a reduction in production allowances. The Montreal Protocol is frequently called the most successful environmental treaty in history, yet its success is based primarily on voluntary compliance by all of the Parties to the treaty. If the United States were to continue ~~production~~ sale and distribution of ODS products after adequate alternative

products were available, this could lead other Parties to do the same, eventually threatening the integrity of the Montreal Protocol. In the words of the Executive Summary cited in the comment, "Failure to comply with the Montreal Protocol would delay or could even prevent recovery of the ozone layer." (Executive Summary at xxv.) The continued existence of a strong Montreal Protocol is in the best interest of the public health of the United States, and our failure to take timely action on albuterol MDIs could potentially weaken the Montreal Protocol.

(Comment 46) One comment criticized our attempts in the 2004 proposed rule to quantify the environmental benefits of this rulemaking.

We agree with the comment that accurately quantifying the direct environmental benefits of this rule is very difficult and that quantifying the indirect environmental benefits may be impossible. However, as we discussed in our response to comment 25, we are under separate legal obligation to examine the broader societal costs and benefits of any rulemaking, including the environmental costs and benefits. Accordingly, the discussion of the environmental costs and benefits of this rule is separate from the determination as to whether the criteria in § 2.125 have been met.

(Comment 47) One comment stated ~~that~~ the amount of CFCs released by MDIs is negligible compared to naturally occurring CFCs.

There are no naturally occurring CFCs. ~~Methyl bromide, another ODS that is significantly less potent than CFC-11 and CFC-12, is both naturally produced and naturally absorbed by the oceans and natural vegetation. It may also be absorbed by soil. Both the gross and net amounts of methyl bromide released by natural sources are not well quantified, and the role of naturally occurring methyl bromide in depletion of the Earth's ozone layer is not well understood. However, we cannot do anything about naturally occurring ODSs; we can only regulate manmade ODSs, and CFCs used in albuterol MDIs represent a significant portion of the ODSs used in the United States. The Clean Air Act directed us to determine which medical products are essential. This determination is not based on the specific amount of CFCs released by certain MDIs, but rather on the criteria set out in § 2.125.~~

(Comment 48) A few comments seemed to confuse CFCs with other greenhouse gases, such as carbon dioxide and nitrous oxide, when stating that MDIs were a minor source of CFCs compared to sources such as power plant and automobile emissions.

While CFCs are considered to be greenhouse gases, we are publishing this rule because the criteria in § 2.125 have been

met, rather than any contribution CFCs may be making towards global warming.

(Comment 49) A few comments stated that MDIs were a minor source of CFCs compared to hair spray and deodorants.

CFCs were banned from deodorants, hair spray, and other cosmetics by the 1978 rule. Cosmetics containing CFCs have not been legally marketed in the United States since April 15, 1979, the effective date of the 1978 rule.

H. Comments on the Analysis of Impacts

(Comment 50) We received several comments about our estimates of the price increases that might result from the proposed rule.

One comment objected to FDA estimates of expected price increases based on the price gap between albuterol CFC MDIs and albuterol HFA MDIs from drugstore.com, because the Web site's market share is small and therefore does not accurately represent market prices. This comment recommended that we use retail cash albuterol MDI prices from IMS Health Inc. (IMS). Another comment took average wholesale prices of albuterol MDIs and inflated them according to average retail markups on albuterol for cash payers of 28.8 percent for branded MDIs and 363.3 percent for generic MDIs. From this, the comment calculated cash payers will pay on average $8.61 more per MDI.

Another comment contended that price increases are of limited importance, because insurers have an incentive to maintain lower copayments for albuterol. Lower copayments would minimize the costs to insurers for emergency department visits, hospitalizations, etc. that result from poorer compliance with albuterol therapy.

A few comments said ~~that~~ individuals eligible for Medicare or Medicaid are unlikely to face higher costs for albuterol as a result of this rule.

We believe that cash albuterol MDI prices best reflect prices paid by the uninsured, and, consistent with the comment, have considered data on retail cash albuterol MDI prices from IMS, which are generally considered to be the best price data available. Although we did use prices from drugstore.com in the 2004 proposed rule,[12] this was done primarily because we did not have rights to use the IMS data when the 2004 proposed rule was being prepared. IMS retail price data reflect the impact on consumers better than other measures such as estimates derived

[12] Although the prices derived from IMS data give us much greater assurance than the prices found on drugstore.com that the numbers we use accurately reflect market prices, in the case of albuterol MDIs the differences in prices are not very significant. The drugstore.com price for generic albuterol CFC MDIs is $13.99, while the weighted average retail price derived from IMS data is approximately $13.50. The drugstore.com prices for VENTOLIN HFA and PROVENTIL HFA are $39.61 and $38.99 respectively, while the weighted average retail price derived from IMS data for albuterol HFA MDIs is $39.50. The drugstore.com prices are those posted on February 10, 2005. See section V.C.6 of this document for more information on the prices derived from IMS data.

from average wholesale cash prices inflated by average retail markups for cash payers.

After reviewing these comments, we continue to believe that the likely price increase will be approximately the current difference in price between generic albuterol CFC MDIs and albuterol HFA MDIs, although competition from IVAX's approved albuterol HFA MDI and other albuterol HFA MDIs that enter the market may lower prices somewhat.

We believe that price increases are an important determinant of access for individuals without insurance, who are likely to pay the full amount of price increases out of their own pockets. Copayments for albuterol MDIs for privately insured individuals may change when this rule goes into effect, but such changes will be determined by their insurers. While copayments are generally higher for branded drugs, they are not necessarily higher for branded drugs that lack a generic alternative. We are unable to predict how average copayments may change as a result of the rule.

We agree with the comments suggesting that individuals eligible for Medicare or Medicaid are unlikely to face higher out-of-pocket costs for albuterol as a result of this rule.

(Comment 51) Comments were submitted about our use of estimates of consumers' response to drug price increases taken from the Goldman article (Ref. 4). One comment noted that

elasticity estimates in the Goldman article were based on a broad range of asthma drugs, many of which differ from albuterol MDIs in important ways. The comment contended that these differences prevent us from drawing meaningful conclusions about how demand for albuterol MDIs will respond to price increases.

A second comment noted that the proposed rule failed to make use of estimates in the Goldman article indicating a price elasticity of demand for asthma drugs as large as -.32.

We recognize the limitations of applying results from the Goldman article to the market for albuterol MDIs, and have sought to characterize fully the associated uncertainty. We believe, however, that focusing on a range of elasticity estimates from -.05 to -.15 is reasonable and appropriate given available information.

We used the Goldman article because it provides recent estimates of how consumer demand for asthma drugs responds to price increases. The article finds that among all users of asthma drugs, a doubling of copayments for asthma drugs reduced drug use by 32%. Among chronic asthma sufferers, use of asthma drugs decreased only 22%. To the extent that asthmatics are more willing to reduce their use of maintenance drugs, such as steroid inhalers, than to reduce their use of rescue drugs, such as albuterol MDIs, the true consumer response to albuterol MDI price increases may be less than the Goldman article suggests.

We acknowledge the potential shortcomings of applying estimates from the Goldman article to the market for albuterol MDIs but, lacking better information upon which to base our estimates, focus on the range of elasticity estimates from -.05 to -.15, the same range focused upon in the proposed rule.

(Comment 52) Several comments sought to place our analysis of impacts in proper historical context by suggesting that the reductions in use that we estimate are small compared with historical variations. One comment noted that ~~the mid-1990's~~ introduction of generic albuterol MDIs to the market for albuterol MDIs in the mid-1990's, and the associated decline in prices, was not associated with any decrease in asthma morbidity.

A second comment noted that the introduction of cheaper generic albuterol MDIs did not result in an increase in consumption of albuterol MDIs, implying that removal of generic albuterol MDIs should not result in a decrease in consumption.

A third comment pointed out that the introduction of generic albuterol MDIs to the market coincided roughly with the entry of therapeutic alternatives such as salmeterol xinafoate, ipatropium bromide, fluticasone propionate, and COMBIVENT, which would have decreased demand for albuterol MDIs at the time lower priced generics became available.

A fourth comment noted that year-to-year fluctuations in demand for albuterol MDIs exceed 1 million units, implying that estimated decreases in albuterol demand are small relative to the market.

We believe it is difficult to draw conclusions about the future albuterol MDI market based on characteristics of the market from the 1990s. Our projected decrease in albuterol MDI sales assumes that, apart from price increases, other determinants of albuterol demand are held constant. In the mid-1990s, several factors that influence albuterol MDI demand changed including the prevalence and incidence of asthma and COPD, and patterns of medical practice. However, the effects of these changes cannot easily be estimated with existing data. For example, changes in asthma prevalence before and after 1997 are complicated by changes in the design of the National Health Interview Survey in 1997. We believe the comment stating that introduction of new asthma drugs at this time decreased demand for albuterol MDIs is probably correct, but we lack the data needed to quantify any decrease in demand caused by introduction of new asthma drugs. Because important determinants of albuterol MDI demand are not held constant, the lack of a clear relationship between aggregate albuterol MDI sales and average prices in the 1990s does not undermine the projection that, all

other factors remaining the same, use of albuterol MDIs will fall as prices rise.

We agree that a reduction in albuterol MDI use of several hundred thousand annually is a small percentage of the total number of albuterol MDIs used in the United States.

I. Other Comments

(Comment 53) Speakers at the PADAC meeting and written comments said ~~that~~ albuterol MDIs were overused and ~~that~~ the phaseout of albuterol CFC MDIs would be an appropriate time for physicians and patients to reevaluate the patients' use of asthma medication. The reevaluation would optimize drug regimens used by asthma patients by emphasizing use of maintenance drugs and deemphasizing the use of albuterol MDIs as a rescue medication. One comment suggested ~~that~~ we incorporate a strategy to encourage these interchanges into this final rule. Another written comment disagreed with these comments, and asserted that the elimination of the essential-use designation for albuterol MDIs should not be viewed as a teachable moment and ~~that~~ it would be inappropriate to force patients to use other longer acting but more expensive drugs by effectively raising the price of albuterol MDIs.

While recognizing that many experts believe that albuterol MDIs are being overused, we do not have any reliable data that show that there is a significant pattern of overuse. In any

case, the overuse or underuse of a drug product is not a factor that we consider under § 2.125(g). We do, however, welcome any opportunity for physicians and patients to reexamine the patients' drug use and to try to optimize the patients' treatment regimens. It is also important to remember that we do not regulate the practice of medicine and any effort on our part to incorporate into our regulation a strategy to encourage these consultations could easily be construed as the regulation of the practice of medicine.

(Comment 54) A comment from an industry organization stated that educating patients and health care providers about the transition from albuterol CFC MDIs to albuterol HFA MDIs is very important, and offered to participate in cooperative education programs with FDA and other interested parties. GSK has outlined their education plans in their comments. ~~The stakeholders group submitted an education plan to the docket.~~ Other comments stated the importance of transition education.

We agree that educating patients and health care providers about the transition is very important. Anyone who wishes to discuss a cooperative educational effort with HHS and FDA should contact ~~the agency~~FDA or the Office of the Secretary of HHS.

(Comment 55) One comment recommended that, in setting an effective date, we take into consideration the time necessary to educate patients and health care providers about the transition

to albuterol HFA MDIs, and one comment recommended more time for this education.

~~While w~~We believe that educating patients and health care providers about the transition to albuterol HFA MDIs is very important~~., we do not believe that it will require substantial amounts of time.~~ From most patients' perspective, albuterol HFA MDIs are essentially identical[13] to the albuterol CFC MDIs they will be replacing. An explanation that an albuterol HFA MDI is being substituted for the albuterol CFC MDI the patient had been receiving and a ~~brief~~ explanation of the ~~minor~~ differences in using the new MDI should be adequate for the vast majority of patients. This explanation can be given by the patient's physician, pharmacist, or other health care provider. While we realize it will take some time to prepare and distribute educational material, we believe that adequate education can easily be provided before the final transition to albuterol HFA MDIs.

(Comment 56) One comment asserted that "a premature phaseout would compromise the reward structure for innovation." The comment also asserted that firms that had made substantial

[13] While PROVENTIL HFA and VENTOLIN HFA can be substituted for albuterol CFC MDIs, they are not therapeutic equivalents to albuterol CFC MDIs, or to each other, as that term is defined in the Orange Book. There are minor differences between the formulations of VENTOLIN HFA and PROVENTIL HFA that might be significant for some small patient subpopulations (see our response to comment_28), but for the vast majority of patients these differences should not be significant.

investments in developing albuterol HFA MDIs would be adequately rewarded for the innovation even if this rule were made effective at a date that would allow generic albuterol HFA MDIs to enter the market before the removal of the essential-use designation for albuterol MDIs. The comment stated that GSK had profited handsomely from sales of its combination fluticasone and salmeterol DPI products in the United States and abroad.

We do not see, nor does the comment explain, how profits from the sale of combination fluticasone and salmeterol DPIs could be seen as a reward for GSK's albuterol HFA MDI research and development. Even if we assume that GSK's sales of other products somehow provide adequate incentives for its innovation, the comment does not assert how the research and development efforts of 3M, the manufacturer of the first albuterol HFA MDI marketed in the United States, have been rewarded.

The development of ozone-friendly products is important to achieving the goal of protection of the Earth's ozone layer. Accordingly, ~~although rewarding companies that developed ozone-friendly products is not a criterion under § 2.125(g),~~ it is a factor we considered in our analyses of impacts (see the 2004 proposed rule at pages 33164-33165 and section V of this document).

(Comment 57) One comment emphasized the importance of encouraging the development of ozone-friendly products and

stated that, in consideration of the pharmaceutical firms developing ODS free alternatives, the U.S. Government had committed itself "to ensure prompt removal of nonessential CFC MDIs as soon as new and reformulated products became available."

As we said before, the development of ozone-friendly products is important to achieving the goal of protection of the Earth's ozone layer. However, we are unaware of the commitment described in this comment. The 2002 final rule and this rulemaking have been undertaken ~~to better comply with the provisions of~~ pursuant to our obligations under the Clean Air Act and the Montreal Protocol.~~, and not because of any sort of contract between ourselves and firms that develop ozone-friendly products.~~

(Comment 58) A few comments expressed unfavorable opinions on salmeterol DPIs and combination fluticasone and salmeterol DPIs. Another comment complained about the high prices of levalbuterol hydrochloride (HCl) inhalation solution.

We have not considered salmeterol DPIs, combination fluticasone and salmeterol DPIs, or levalbuterol HCl inhalation solution to be ~~an~~ alternatives to albuterol CFC MDIs. Comments about salmeterol DPIs, combination fluticasone and salmeterol DPIs, and levalbuterol HCl inhalation solution are not relevant to this rulemaking.

IV. Environmental Impact

We have carefully considered the potential environmental effects of this action. We have concluded that the action will not have a significant adverse impact on the human environment, and that an environmental impact statement is not required. Our finding of no significant impact, and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Division of Dockets Management (see ADDRESSES) between 9 a.m. and 4 p.m., Monday through Friday.

V. Analysis of Impacts

A. Introduction

We have examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), the Unfunded Mandates Reform Act of 1995 (Public Law 104-4), and the Congressional Review Act. Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. This final rule is considered an economically significant regulatory action under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. We lack the data to certify that this final rule will not have a significant economic impact on a substantial number of small entities. Therefore, we have prepared a Regulatory Flexibility Analysis.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before issuing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $115 million, using the implicit GDP deflator for 2003, the most recent year for which final data exist. This rule, however, does not contain such a mandate.

The Congressional Review Act requires that regulations that have been identified as being major must be submitted to Congress before taking effect. This rule is major under the Congressional Review Act.

Limitations in the available data prevent us from estimating quantitatively the anticipated costs and benefits to society, so we focus instead on proxy measures. The costs of

this final rule include the benefits lost by consumers who would have bought albuterol MDIs at the current price but are unwilling or unable to buy them at a higher price. The price of albuterol MDIs will rise because this rule, by ending the essential-use designation for albuterol MDIs, will effectively remove less expensive generic versions of albuterol MDIs from the market. Consumers and third-party payers, including Federal and State Governments, will spend more for albuterol MDIs as a result of the price increase. But this increased spending is not part of social cost as conventionally defined, because it represents resources that are transferred from drug buyers (consumers and third-party payers) to drug sellers (drug manufacturers, wholesalers, pharmacies, etc.). The benefits of this rule include the value of improvements in the environment and public health that may result from reduced emissions of ODSs (for example, the reduced future incidence of skin cancers and cataracts). The benefits also include improved expected returns on investments in environmental technologies and greater international cooperation to comply with the Montreal Protocol. As we are unable to estimate the costs and benefits in dollar terms, we instead focus on the cumulative number of albuterol MDIs that might not be sold and the changes in CFC emissions as a result of the rule.

As a result of this rule, approximately 96 million to 430 million albuterol CFC MDIs will be removed from the market, depending on when generic albuterol MDIs become available. If generic albuterol HFA MDIs enter the market at the end of 2010 (when one of the earlier listed patents for albuterol HFA MDIs expires) 96 million albuterol CFC MDIs would have been sold between the effective date of this rule (December 31, 2008) and the end of 2010, without the rule. ~~. These~~ If generic albuterol HFA MDIs enter the market at the end of 2017 (when the last listed patent for albuterol HFA MDIs expires) 430 million albuterol CFC MDIs would otherwise have been sold between the effective date of this rule ~~(December 31, 2008)~~, ~~and when the last listed patent for albuterol HFA MDIs will have expired in~~ and December 2017, without the rule. After generic albuterol HFA MDIs enter the albuterol MDI market and competition among ~~them~~ albuterol HFA MDI producers determines the price, there would be no rationale related to patient access to albuterol MDIs for maintaining an essential-use designation for ODSs for albuterol.

Assuming generic albuterol HFA MDIs enter the market at the end of 2010, the removal of albuterol CFC MDIs will eliminate competition from low-cost generic drugs during the period between December 2008 and December 2010, thereby raising prices and increasing spending on albuterol MDIs by about $2.1 billion,

assuming a 3 percent discount rate, or $1.7 billion, assuming a 7 percent discount rate (present value in 2005).

Assuming generic albuterol HFA MDIs enter the market at the end of 2017, t~~T~~he removal of albuterol CFC MDIs will eliminate competition from low-cost generic drugs during the period between December 2008 and December 2017, thereby raising prices and increasing spending on albuterol MDIs by about $8.3 billion, assuming a 3 percent discount rate, or $6.2 billion, assuming a 7 percent discount rate (present value in 2005).

Taking into account GSK's commitment to provide free samples and coupons, we estimate that higher prices due to the elimination of generic competition will reduce the number of albuterol MDIs sold by between 300,000 and 900,000 per year. This ~~The price increase~~ will induce U.S. consumers to use between 600,000 and 1.8 million fewer albuterol MDIs between December 31, 2008 and December 2010, or to use 2.7 million and 8.1 million fewer albuterol MDIs during the years between the removal of albuterol CFC MDIs on December 31, 2008, and December 2017. ~~Taking into account GSK's commitment to provide free samples and coupons, we estimate that higher prices due to the elimination of generic competition will reduce the number of albuterol MDIs sold by between 300,000 and 900,000 per year.~~ These~~is~~ estimates do~~es~~ not take into account the GSK and Shering patient assistance programs designed to provide free or low cost drugs to low-

income patients. Should generic albuterol MDIs become available at the end of 2010, consumers will substitute 96 million albuterol HFA MDIs for albuterol CFC MDIs between 2008 and December 2010, reducing atmospheric CFC emissions by 2,400 tons in total. If generic albuterol MDIs become available at the end of 2017, ~~S~~substitution of albuterol HFA MDIs for the 430 million albuterol CFC MDIs that would have been consumed between 2008 and December 2017 will reduce atmospheric emissions of CFCs by about 10,800 tons in total. These quantitative estimates of the effects of this rule are summarized in tables 1 and 2.

Table 1.--Summary of Quantifiable Effects of the Final Rule Relative to HFA Patent Expiration in 2010

Number of Affected Albuterol MDIs (millions)	Increased Expenditures for Albuterol MDIs Present Value in 2005 (billions)		Possible Reduction in MDI Use (millions)	Reduced Aggregate Emissions Related to Phaseout (metric tons)
96 million	3-percent discount rate	7-percent discount rate	0.6 to 1.8	2,400
	$2.1	$1.7		

Table ~~1~~2.--Summary of Quantifiable Effects of the Final Rule Relative to HFA Patent Expiration in 2017

Number of CFC Albuterol MDIs Removed From the Market	Increased Expenditures for Albuterol MDIs Present Value in 2005 (billions)		Possible Reduction in MDI Use (millions)	Reduced Aggregate Emissions Related to Phaseout (metric tons)
430 million	3-percent discount rate	7-percent discount rate	2.7 to 8.1	10,800
	$8.3	$6.2		

While the agency believes that the benefits of this regulation justify its costs, we cannot estimate quantitatively the public health effects of the phaseout. The decreased use of albuterol MDIs may adversely affect some patients, but we lack

an ability to characterize such effects quantitatively. We also are unable to estimate quantitatively the reductions in skin cancers, cataracts, and environmental harm that may result from the reduction in CFC emissions by 10,800 metric tons during these years.

We state the need for the regulation and its objective in section V. B of this document. Section V.C of this document provides background on CFC depletion of stratospheric ozone, the Montreal Protocol, the albuterol MDI market, and the health conditions that albuterol is used to treat. We analyze the benefits and costs of the rule, including effects on government outlays, in section V.D of this document. We assess alternative phaseout dates in section V.E of this document, and conduct a sensitivity analysis on entry dates of generic competition in section V.F of this document. We present an analysis of the effects on small business in a regulatory flexibility analysis in section V.G of this document. We discuss our conclusions in section V.H of this document.

B. Need for Regulation and the Objective of this Rule

This regulation is necessary because private markets are very unlikely to preserve levels of stratospheric ozone sufficient to protect the public health. Individual users of albuterol MDIs have no significant private incentive to switch to non-ozone depleting albuterol HFA MDIs. In fact, each user

would bear all of the costs and virtually none of the benefits of such a switch, as the environmental and health benefits would tend to be distributed globally and occur decades in the future. Thus, the outcome of a private market would be continued use of the albuterol MDI available at the lowest price, even if the social value of reducing emissions were clearly much greater than the price premium for non-ozone depleting albuterol HFA MDIs.

~~This regulation is also necessary to comply with the requirements of the Montreal Protocol in an efficient manner.~~

The objective of this final rule is to reduce atmospheric emissions of ODSs, specifically CFCs. CFCs and other ODSs deplete the stratospheric ozone that protects the Earth from ultraviolet solar radiation. We are ending the essential-use designation for ODSs used in albuterol MDIs because two acceptable ODS-free albuterol formulations have been successfully marketed in the United States for more than 2 years. Removing this essential-use designation will comply with obligations under the Montreal Protocol and the Clean Air Act, thereby reducing emissions that deplete stratospheric ozone, while preserving access to essential drugs by minimizing adverse effects on affected patient populations.

C. Background

1. CFCs and Stratospheric Ozone

During the 1970s, scientists became aware of a relationship between the level of stratospheric ozone and industrial use of CFCs. Ozone (O_3), which causes respiratory problems when it occurs in elevated concentrations near the ground, shields the Earth from potentially harmful solar radiation when in the stratosphere. Excessive exposure to solar radiation is associated with adverse health effects such as skin cancer and cataracts, as well as other adverse environmental effects. Emissions of CFCs and other ODSs reduce stratospheric ozone concentrations through a catalytic reaction, thereby allowing more solar radiation to reach the Earth's surface. Because of this, environmental scientists from the United States and other countries advocated ending all uses of these chemicals.

2. The Montreal Protocol

The international effort to craft a coordinated response to the global environmental problem of stratospheric ozone depletion culminated in the Montreal Protocol, an international agreement to regulate and reduce ~~use~~ production of ODSs. The Montreal Protocol is described in section III.B of this document. One hundred and eighty-six countries have now ratified the Montreal Protocol, and the overall usage of CFCs has been dramatically reduced. In 1986, global consumption of CFCs totaled about 1.1 million metric tons annually, and by

2000, total annual consumption had been reduced to fewer than 0.1 million metric tons (Ref. 5). This decline amounts to about a 90-percent decrease in consumption and is a key measure of the success of the Montreal Protocol. Within the United States, consumption of ODSs, and CFCs in particular, has fallen sharply--consumption of CFC-11 and CFC-12 is about 20 percent of 1990 consumption.[14]

A ~~key~~ relevant aspect of the Montreal Protocol is that ~~use~~production of ~~ODSs~~ CFCs in any year by any country is banned after the phase-out date unless the Parties to the Montreal Protocol agree to designate ~~it~~ the use as "essential~~.~~" and approve a quantity of new production for that use. Each year, each Party nominates the amount of ~~ODS~~ CFCs needed for each essential use and provides the reason why such use is essential. Agreement on both the essentiality and the amount of CFCs needed ~~of~~ for each nominated use ~~ion~~ has been reached by consensus at the annual Meeting of the Parties.

3. Benefits of the Montreal Protocol

EPA has generated a series of estimates of the environmental and public health benefits of the Montreal Protocol (Ref. 6). The benefits include reductions of hundreds of millions of nonfatal skin cancers, 6 million fewer fatalities

[14] The ozone depleting potentials of CFC-11 and CFC-12 are equal. See

due to skin cancer, and 27.5 million cataracts avoided between 1990 and 2165 if the Montreal Protocol were fully implemented. EPA estimates the value of these and related benefits to equal $4.3 trillion in present value when discounted at 2 percent over the period of 175 years. This amount is equivalent to about $6 trillion after adjusting for inflation between 1990 and 2004. This estimate includes all benefits of total global ODS emission reductions expected from the Montreal Protocol and is based on reductions from a baseline scenario in which ODS emissions would continue to grow for decades but for the Montreal Protocol.

4. Characteristics of COPD

Albuterol MDIs are used to treat COPD. While there is some overlap between asthma patients and COPD patients, COPD encompasses a group of diseases characterized by relatively fixed airway obstruction associated with breathing-related symptoms (for example, chronic coughing, expectoration, and wheezing). COPD is generally associated with cigarette smoking and is extremely rare in persons younger than 25.

According to the Centers for Disease Control (CDC), an estimated 10 million U.S. adults carried the diagnosis of COPD in 2000 (Ref. 7). Because the underlying surveys depend on patient-reported diagnoses and many affected individuals have

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http://www.epa.gov/ozone/ods.html.

not been formally diagnosed, the National Health Interview Survey (NHIS) suggests that as many as 24 million Americans may actually be affected by the disease. The proportion of the U.S. population with mild or moderate COPD has declined over the last quarter century, although the rate of COPD in females increased relative to males between 1980 and 2000. The most effective intervention in modifying the course of COPD is smoking cessation. Symptoms such as coughing, wheezing, and sputum production are treated with medication.

5. Characteristics of Asthma

Albuterol MDIs are also used to treat asthma, a chronic respiratory disease characterized by episodes or attacks of bronchospasm on top of chronic airway inflammation. These attacks can vary from mild to life-threatening and involve shortness of breath, wheezing, cough, or a combination of symptoms. Many factors, including allergens, exercise, viral infections, and others, may trigger an asthma attack.

According to the 2002 National Health Interview Survey (NHIS), approximately 20 million patients in the United States reported they had asthma (Ref. 8). The prevalence of asthma decreases with age, with the prevalence being 92 per 1,000 children ages 0-17 (6.1 million children) compared to 83 per 1,000 among adults ages 18-44 (7.4 million), 71 per 1,000 among

adults ages 45-64 (4.6 million), and 59 per 1,000 among adults age 65 and over (1.9 million) (Ref. 8).

The NHIS reported that during 2002, about 12 million patients reported experiencing an asthma attack during the previous year (Ref. 8, table 10). According to the National Ambulatory Medical Care Survey, in 2001 there were 1.3 million outpatient asthma visits to physician offices and hospital clinics and 1.9 million emergency room visits (Ref. 8, table 16). According to the National Center for Health Statistics, there were 454,000 hospital admissions for asthma in 2001 (Ref. 8, table 12), and 4,269 mortalities (Ref. 8, table 1). The estimated direct medical cost of asthma (hospital services, physician care, and medications) was $9.4 billion (Ref. 8, table 17).

While the prevalence of asthma has been increasing in recent years, the CDC reports that the incidence of asthma (or the rate of new diagnoses) has remained fairly constant since 1997 (Ref. 9). Non-Hispanic blacks, children under 17 years old, and females have higher incidence rates than the general population and also have higher attack prevalence. The CDC notes that although numeric increases have occurred in the numbers and rates of physician office visits, hospital outpatient visits, and emergency room visits, these increases

are accounted for by the increase in prevalence. This phenomenon might indicate early successes by asthma intervention programs that include access to medications.

6. Current U.S. Albuterol MDI Market

Albuterol is the preferred, and most commonly prescribed, short-acting relief medication for asthma and is also important in the treatment COPD. For reasons of cost, convenience, and effectiveness, MDIs are the preferred, and most commonly prescribed, route of administration for albuterol.

We estimate that, in the first two quarters of 2004, U.S. consumers bought about 22.7 million generic albuterol MDIs through retail channels. This estimate is based on our analysis of IMS data (~~analysis of IMS data~~Ref. 10).[15] Total consumption of albuterol MDIs has fluctuated around approximately 50 million MDIs annually over the last several years (Ref. 11~~0~~). Based on retail sales, we estimate approximately 96 percent of albuterol MDIs sold were generic MDIs or branded MDIs relabeled and sold as generic (~~analysis of IMS data~~Ref. 10) (all containing CFCs), suggesting a total market for generic albuterol MDIs of approximately 48 million MDIs.

[15] Analysis completed by FDA based on information provided by IMS Health, IMS National Prescription Audit™, 2004; IMS Health, IMS MIDAS™, Q1/2004--Q2/2004.

IMS provides data on average retail prices for marketers of albuterol MDIs for each of three payer types (cash customers, Medicaid recipients, and patients covered by other third-party payers), and the proportion of each marketer's sales to each payer type. As described in table ~~2~~3 below, the weighted average (across all payer types) of retail prescription price for generic albuterol CFC MDIs during the first half of 2004 was about $13.50 per MDI, the weighted average retail prescription price for branded versions of albuterol CFC MDIs was about $38.90 per MDI, and the weighted average retail prescription price for albuterol HFA MDIs was about $39.50 per MDI.

Table ~~2~~3.--Summary of Current Retail Prices for Albuterol CFC and HFA MDIs

Payer Type	Generic Market Share (percent)	Albuterol CFC MDI Prices		Albuterol HFA MDI Prices	Price Premium: HFA MDI Price Relative to Generic Price		Estimated Units (millions) *
		Generics	Weighted Average Branded Products	Weighted Average	Dollars per MDI	Percent	
Cash	97.0	$19.13	$45.90	$46.32	$27.19	142	5.2
Medicaid**	97.3	$15.61	$37.10	$41.14	$25.53	164	8.7
Third-party	95.4	$12.03	$37.75	$38.60	$26.57	221	31.4
Total Market	96.0	$13.53	$38.87	$39.47	$25.94	192	45.3

* These estimates reflect retail sales of generic albuterol MDIs, excluding sales at internet and mail-order pharmacies.

**Medicaid prices do not reflect rebates given directly to States by drug companies.

Source: ~~Analysis of IMS data~~(Ref. 10)

—We estimate albuterol CFC MDIs are responsible for roughly 1,200 metric tons of CFC emissions annually. Each albuterol CFC MDI contains about 21 grams of CFCs.[16] The estimated 48 million albuterol CFC MDIs sold annually therefore contain about 1,000 metric tons of CFCs. Adding an additional 20 percent to account for use in production, unusable batches, and other factors (as manufacturers typically do in the process of requesting essential-use allocations of CFCs for manufacturing) brings the total emissions to about 1,200 metric tons. To the extent that CFCs used in the production process are reclaimed and destroyed, this estimate overstates expected emissions reductions.

D. Benefits and Costs of the Final Rule

The benefits and costs of a government action are conventionally estimated relative to a baseline scenario that in this case is a description of the production, use, and access to albuterol MDIs in the absence of this rule. In this section we first describe such a baseline and then present our analysis of the benefits of the final rule. Next we turn to the costs of the rule and to an analysis of the effects on the Medicare and Medicaid programs.

1. Baseline Conditions

[16] CFC MDI manufacturers disclose the CFC content of their MDIs to EPA as part of the process of requesting essential-use allocations; however, the CFC content of any particular MDI is considered confidential business information and may not be disclosed without the manufacturer's consent.

We developed baseline estimates of future conditions to estimate the economic effects of prohibiting marketing of albuterol CFC MDIs after December 31, 2008. It is standard practice to use, as a baseline, the state of the world absent the rulemaking in question, or where this implements a legislative requirement, the world absent the statute.

For the baseline in this analysis, we assume that access to CFC propellants, and therefore to albuterol CFC MDIs, continues indefinitely. This assumption focuses our analysis on the impact of removing less expensive generic albuterol CFC MDIs from the market, until the date that competition from generic albuterol HFA MDIs lowers prices. As stated earlier, we have identified listed patents on the HFA technology with expiration dates of 2009, 2010, 2014, 2015, and December 2017. We have assumed that listed patents are valid, that all listed patents would be infringed by any generic albuterol HFA MDI, and that generic albuterol HFA MDIs will be available at, but not sooner than, the end of 2017. In a sensitivity analysis presented below, we evaluate the effects of patent expiration dates of 2010 and 2015.

Without this rule, U.S. commitments to the Montreal Protocol ~~c~~would likely limit future access to CFCs and, therefore, inexpensive generic albuterol CFC MDIs. This

observation suggests an alternative baseline where Parties to the Montreal Protocol stop approving nominations for the use of CFCs in albuterol MDIs at a particular date. While the Parties could ~~plausibly~~ theoretically take such action for calendar year 2008, it would be speculative on our part to assume that they would take such action for that specific date or any other. As a result, we do not pursue a quantitative analysis with such alternative baselines. ~~We note in passing, however, that if the Parties to the Montreal Protocol decided to approve a U.S. nomination of CFCs for albuterol MDIs to be an essential use in 2007 but not 2008 or subsequently, then the rule would have negligible costs and benefits. In this case, existing inventories of CFCs (if carried into the future) would provide for low-cost albuterol MDIs for 2008.~~

Throughout our analysis, we assume that future prices for albuterol CFC and HFA MDIs do not change from current levels. This assumption overstates prices to the extent that competition from new entrants reduces future albuterol HFA MDI prices. We assume, however, that competition among the albuterol HFA MDI manufacturers will leave prices roughly stable and note that one manufacturer has pledged to freeze prices until at least the beginning of 2008.

Throughout this analysis, we assume that sufficient inventories of CFCs are available to meet demand up to December 31, 2008, and that albuterol HFA MDIs available on and after December 31, 2008, will be adequate to meet demand. In calculating the present value of increased expenditures, we discount expected future increases in expenditures by both 7 percent and 3 percent annually for each year after 2005.

2. Benefits of the Final Rule

The benefits of the final rule include environmental and public health improvements from protecting stratospheric ozone by reducing CFC emissions. Benefits also include expectations of increased returns on investments in environmentally friendly technology, reduced risk of unexpected disruption of supply of albuterol MDIs, and continued international cooperation to comply with the spirit of the Montreal Protocol, thereby potentially reducing future emissions of ODS throughout the world.

a. Reduced CFC emissions. Market withdrawal of albuterol CFC MDIs will reduce emissions by approximately 1,200 metric tons of CFCs per year ~~after December 21, 2008~~. We have reviewed current CFC inventories and believe currently available quantities are likely to be sufficient to supply the albuterol CFC MDI market for approximately 12 months. Nominations ~~that~~

~~might add to inventories~~ for new CFC production are generally approved by the Parties to the Montreal Protocol 2 years in advance. The final rule bans marketing of albuterol CFC after December 31, 2008. ~~We expect CFC nominations for 2007 to be the last.~~ There is considerable uncertainty with respect to the amount of inventories that will be available in the future, but we anticipate that utilization of existing inventory will allow the United States to avoid requesting a 2008 exemption, or to significantly reduce the amount requested. ~~We expect CFC inventories available at the end of 2007 to be exhausted by the end of 2008, the point at which the manufacture of albuterol CFC MDIs would no longer be possible.~~ Therefore, we estimate the final regulation will reduce CFC use by 1200 metric tons per year after the end of 2008, a benefit that will continue beyond the evaluation period.

In an evaluation of its program to administer the Clean Air Act, EPA has estimated that the benefits of controlling ODSs under the Montreal Protocol are the equivalent of $6 trillion in current dollars. However, EPA's report provides no information on the total tons of reduced emissions or the incremental value per ton of reduced emissions. EPA derived its benefits estimates from a baseline that included continued increases in emissions in the absence of the Montreal Protocol. We have searched for authoritative scientific research that quantifies

the marginal economic benefit of incremental emission reductions under the Montreal Protocol, but have found none conducted during the last 10 years. As a result, we are unable to quantify the environmental and human health benefits of reduced ODS emissions from this regulation. Such benefits, in any event, were apparently included in EPA's earlier estimate of benefits.

As a share of total global emissions, the reduction associated with the elimination of albuterol CFC MDIs represents only a small fraction of 1 percent. Current allocations of CFCs for albuterol MDIs account for about 0.1 percent of the total 1986 global consumption of CFCs (Ref. 5). Furthermore, current U.S. CFC emissions from MDIs represent a much smaller, but unknown share of the total emissions reduction associated with EPA's estimate of $6 trillion in benefits because that estimate reflects future emissions growth that has not occurred.

Although the direct benefits of this regulation are small relative to the overall benefits of the Montreal Protocol, we believe the reduced exposure to UV-B radiation that will result from these reduced emissions will help protect public health. However, we are unable to assess or quantify specific reductions in future skin cancers and cataracts associated with these reduced emissions.

b. Returns on investment for environmental technology. Establishing a ~~fairly early~~ phaseout date prior to the expiration of patents on albuterol HFA MDIs not only rewards the developers of the HFA technology, but also serves as a signal to other potential developers of ~~environmentally benign~~ ozone-safe technologies. In particular, ~~a relatively early~~ such a phaseout date would preserve expectations that that the government protects incentives to research and develop ~~environmentally benign~~ ozone-safe technologies.

Newly developed technologies to avoid ODS emissions have resulted in more environmentally "friendly" air conditioners, refrigerants, solvents, and propellants, but only after significant investments. Several manufacturers have claimed development costs that total between $250 million and $400 million to develop HFA MDIs and new propellant-free devices for the global market (Ref. 11~~0~~).

These investments have resulted in several innovative products in addition to albuterol HFA MDIs. For example, breath-activated delivery systems, dose counters, dry powder inhalers, and mini-nebulizers have also been successfully marketed. This technology could also affect other drugs used for the treatment of asthma and COPD because of the likelihood that, eventually, CFCs will not be available for any drug use.

To compare the effect of alternative phaseout dates on these returns to investment, we compare the ratio of the present value of increased revenues expected to accrue to innovative firms from a December 31, 2008, phaseout date and the present value of the future revenue stream of alternative phaseout dates, using both 7 percent and 3 percent annual discount rates. This ratio can provide a basis for relative assessments of the returns to investors for alternative phaseout dates. We present estimates of this ratio in a later discussion of alternatives.

Returns on investment are very sensitive to the current market prices in the United States. The pharmaceutical markets of other Parties to the Montreal Protocol operate with implicit or explicit price controls. These controls have depressed the potential returns to technological innovation. For example, in 2003, the ex-manufacturer prices (the prices of the drugs when they leave the production facilities) of the albuterol HFA MDIs most widely sold in France, Germany, and the United Kingdom ranged between roughly $3.30 and $6.4~~30~~; in the United States these prices were in the neighborhood of $29 to $30.[17]

c. International cooperation. The advantages of selecting a date that maintains international cooperation are substantial because the Montreal Protocol, like most international

environmental treaties, relies primarily on a system of national self-enforcement, although it also includes ~~significant trade sanctions~~ has a mechanism to address ~~for~~ noncompliance. In addition, compliance with its directives is subject to differences in national implementation procedures. Economically less-developed nations, which have slower phaseout schedules than developed nations, have emphasized that progress in eliminating ODSs in developing nations is affected by observed progress by developed nations, such as the United States. If we had adopted a later phaseout date, other Parties could ~~decide~~ attempt to delay their own control measures.

3. Costs of the Final Rule

The effects of the final rule include increased spending for needed albuterol medication. The social costs of the final rule include the lost benefits of albuterol use that may result from the price increase. We discuss the increased spending and then the social costs in turn.

In the absence of this regulation, we would expect 430 million generic albuterol MDIs to be sold during the entire period between December 31, 2008, and December 2017, when the last patent listed in Orange Book for an albuterol HFA MDI will expire. This figure is based on the estimate that approximately

[17] Analysis completed by FDA based on information provided by IMS Health, IMS

96 percent (~~analysis of IMS data~~Ref. 10) of the approximately 50 million albuterol MDIs sold per year (Ref. 11~~0~~) are generic, suggesting that about 48 million generic albuterol MDIs are sold annually.

With this regulation, patients who would have used generic albuterol CFC MDIs are expected generally to switch to albuterol HFA MDIs. We estimated in section V.C.6 of this document a weighted average price difference at retail pharmacies (across all payer types) of about $26 between these products. If this difference can be applied to future transactions involving 48 million generic albuterol MDIs annually (less the 2 million free samples promised by GSK and decreased demand of 300,000 to 900,000 MDIs resulting from price increases--as calculated later in this analysis), then increased expenditures from consumers and private or public third-party payers would reach about $1.2 billion per year. This estimate is based, in part, on estimated increases in Medicaid prices that do not take into account rebates given directly to States by drug companies. To the extent that such rebates are larger for branded albuterol MDIs, which are more expensive, the increased expenditures are overestimated.

MIDAS™, U.S., Germany, France and the United Kingdom, 2003.

The present value of these increased expenditures in 2005 is about $6.2 billion using a 7 percent annual discount rate and $8.3 billion using a 3 percent annual discount rate. In estimating this increased spending, we focus on the period between December 31, 2008, and December 2017, when the last patent listed in Orange Book will expire. We also ignore the fact that after a VENTOLIN HFA MDI is first used, it expires much more quickly than a PROVENTIL HFA MDI or albuterol CFC MDIs. Although this change in the usable life of some MDIs may affect the quantity consumed, we are unable to quantify the magnitude of such an effect.

These increased expenditures represent primarily transfers from consumers and third-party payers, including State and Federal Governments, to branded pharmaceutical manufacturers; they are, therefore, not net costs to society. Because these estimates are based on average retail prices, they include additional spending that will go to parties other than innovative manufacturers, such as distributors and retail pharmacies. We estimate that about 11 percent of this increase--about $130 million annually--may be paid by uninsured customers ($130 million) (~~analysis of IMS data~~Ref. 10). We derive these estimates assuming increased spending is the product of the number of albuterol MDIs sold for cash and the difference between the average price for generic albuterol MDIs and the

simple mean of the prices for albuterol HFA MDIs. We estimate that 5 million generic albuterol MDIs are sold to uninsured patients annually and that retail cash prices for albuterol MDIs will rise by about $27 per MDI (details of these estimates follow later in this section.) Taking in to account savings from coupons and free samples, uninsured albuterol users would therefore spend about $120 million more each year.[18]

According to MEPS, private nongroup and uninsured individuals used, on average, 3.3 albuterol prescriptions per year (Ref. 12~~1~~). Based on IMS data, we estimate the average albuterol prescription is for 1.2 MDIs (~~analysis of IMS data need clearance~~Ref. 10). The average uninsured, or underinsured, albuterol user would therefore use about 4 MDIs/year. Based on these figures, we estimate that a population of uninsured albuterol users of about 1.25 million[19] would pay, on average, $95 more per year for albuterol.[20] This estimate does not take in to account the reduced use of albuterol MDIs among the uninsured that may result from higher prices or the extent to which quicker expiration of some HFA albuterol MDIs, relative to CFC MDIs, will increase albuterol MDI demand and expenditures.

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[18] (5 million MDIs - 300,000 free sample MDIs) x ($25/MDI) - (450,000 coupons) x ($10) = $117,500,000. Here, we assume coupons and free samples reach uninsured albuterol users in proportion to estimates of the uninsured fraction of the overall population (15 percent).

[19] (5 million MDIs) / 4 MDIs per uninsured user = 1.25 million uninsured users.

In the future, some fraction of these cash payers will likely be covered by Medicare (~~analysis of IMS data~~Ref. 10).

We expect price increases resulting from market withdrawal of less expensive generic albuterol MDIs will reduce albuterol use by several hundred thousand MDIs annually (as explained below), although there is substantial uncertainty about these estimates. The impact of this reduction on health outcomes is too uncertain to quantify given available data. Some patients, however, respond to price increases for medications for chronic conditions in ways that may adversely affect their health. A recent article found that:

> copayment increases led to increased use of emergency department visits and hospital days for the sentinel conditions of diabetes, asthma, and gastric acid disorder: predicted annual emergency department visits increased by 17 percent and hospital days by 10 percent when copayments doubled * * *.

However, the article proceeds to characterize these results as "not definitive." (Ref. 4) This finding suggests that increased prices for albuterol may lead to some adverse public health effects among the populations that would face increased prices. This evidence is insufficient to permit us to quantify any adverse public health effects. We use expected reductions in albuterol MDI purchases as a surrogate measure of the impact.

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[20] ($117,500,000) / (1.25 million uninsured users) = $94.00 per uninsured

Our approach to estimating the effects of the rule assumes that the primary effect of an elimination of albuterol CFC MDIs from the market would be an increase in the average price of albuterol MDIs. Given the price increase expected from the elimination of generics and existing estimates of market responses to price increases, we have projected how the quantity of albuterol MDIs consumed may decline as a result of this rule. As in the proposal, we assume that the reduction in the use of albuterol MDIs attributable to this rule can be calculated as the product of the sensitivity of use with respect to the price increase, the baseline use of albuterol MDIs among price-sensitive patients, and the price increase in percentage terms. We discuss these in turn.

We have no information about how consumers react to increases in the price of MDIs per se or to increases in the price of "rescue" types of MDIs, such as albuterol, in particular. Economists have researched the response of consumers to higher insurance copayments for drugs in general. The results appear to indicate price elasticities in the range of -.1 to -.2, meaning that a 10 percent increase in insurance copayments appears to lead to a reduction in the number of prescriptions of between 1 and 2 percent (Ref. 132). Some researchers have reported estimates of price elasticities as

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user.

great as -.3 for asthma drugs (Ref. 4), but the authors report that there is wide variance based on the availability of over-the-counter substitutes. For example, for drugs with no over-the-counter substitute--a set that presumably includes albuterol--the reported price elasticity was -.15.[21] We have used price elasticities of between -.05 and -.15 to estimate the potential effect of price increases on demand. We recognize that elasticity estimates derived from insurance copayment studies may not be specifically applicable to the effects of average retail price increases on uninsured patients' demand for albuterol.

To derive an estimate of the number of albuterol MDIs not sold as a result of this rule, we need an estimate of the baseline use of albuterol MDI sales by price-sensitive consumers. From data on retail sales by payer type from the first half of 2004, we find about 5 million generic albuterol MDIs are sold to uninsured patients annually. This estimate includes sales to people over age 65 not covered by Medicaid who we expect will be covered by Medicare in the future, but it excludes mail order and Internet sales and sales through hospitals and nursing homes. Alternatively, if uninsured

[21] Some patients may view PRIMATENE, an epinephrine MDI available over the counter, as a substitute for prescription albuterol MDIs. If this view is widespread, the decline in albuterol MDI use may be greater than that estimated here. However, insofar as PRIMATENE is effective in treating

individuals under age 65 use albuterol MDIs in proportion to their share of the population (roughly 15 percent) (Ref. 143), then roughly 7 million of 46 million generic albuterol MDIs would be sold to the uninsured (46 million = 48 million generic albuterol MDIs - 2 million free samples).

Finally, to estimate the price increase from this rule, we first assess IMS data, which indicate that cash payers paid, on average, $19.10 for generic albuterol MDIs and $46.30 for albuterol HFA MDIs, a difference that would suggest a price increase of $27.20 per MDI, or 142 percent. However, alternative assumptions about the future market share of different albuterol HFA MDI manufacturers would result in a smaller price increase--130 percent. These estimated price differences faced by cash payers are only a proxy for price differences faced by uninsured patients, because some people with insurance may pay cash, and some uninsured patients may buy drugs from mail-order and Internet pharmacies.

We believe that estimates of the recent price premium for albuterol HFA MDIs may be a reasonable approximation of the price increase anticipated from this rule, at least to the extent that patent protection and the more costly criteria for FDA approval of albuterol HFA MDIs substantially curb

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asthma, the adverse health effects would not be greater. We lack data to evaluate patients' willingness to substitute PRIMATENE for albuterol MDIs.

competition. At least one listed patent is expected to expire in December 2017. While increased competition from new patented albuterol HFA MDIs may reduce future albuterol HFA MDI prices, to the extent that all albuterol HFA MDI manufacturers manufacture under a single patent, such reduction may be small. Apart from any patents, marketing of new albuterol HFA MDIs before the patents expire requires FDA approval of a completed NDA. After the patents expire, FDA can approve generic albuterol HFA MDIs by the abbreviated new drug application (ANDA) process. The NDA process is more complicated, expensive, and time consuming than the abbreviated new drug application (ANDA) process by which new generic drugs are brought to market. This NDA requirement constitutes a barrier to entry in the market that will tend to further limit competition until the patents expire as compared to markets where generic drugs can be marketed. Finally, as noted earlier, one manufacturer has also announced a voluntary price freeze on its albuterol HFA MDI until 2008.

We combine different measures of price elasticities (-.05 to -.15), the size of the uninsured generic albuterol MDI market (5 to 7 million MDIs), and estimated price increases (130 percent to 140 percent) to estimate the impact of price increases on use. For example, assuming a price elasticity of - .15 and 6 million generic albuterol MDIs sold to the uninsured

annually, a 130 percent price increase would reduce demand for albuterol MDIs from the uninsured by about 1.2 million MDIs annually (6 million x -.15 elasticity x 130 percent price increase = 1,200,000 MDIs). These preliminary estimates do not take into account offsetting increases in consumption from changes in promotional efforts already announced by GSK. We also note that the elasticity estimates are based on relatively small price changes and may not be applicable to large price changes such as these.

Manufacturers have announced programs to distribute free samples and coupons to mitigate any adverse effect of higher prices on utilization. For example, GSK has committed to provide 2 million albuterol HFA MDIs each year to physician offices in expectation that they would be distributed to patients in need (03P-0029/CR1, p. 7). In addition, GSK has committed to annually providing 3 million coupons worth $10 each in rebates for VENTOLIN HFA to any patient. Both GSK and Schering currently operate outreach programs that assist patients to obtain needed medications, but we are unable to assess how many albuterol MDI users are currently helped by these programs or how many more would be helped in the future.

Free samples and coupons help mitigate adverse impacts on uninsured patients only to the extent that they are distributed

to physicians and other health care professionals who then give them to uninsured individuals.[22] To assess how free samples and coupons might affect albuterol MDI use, we conducted a thorough review of the relevant peer-reviewed literature and found two pertinent articles. One found that, while 54 percent of the free samples were actually distributed to patients, only 9 percent of the patients who received free samples were uninsured (Ref. 154). These data suggest that 4.8 percent of the free samples were actually distributed to uninsured patients. Assuming this estimate is applicable to the albuterol HFA MDIs distributed by the GSK program, then about 96,000 albuterol HFA MDIs per year would reach the uninsured. The second article estimated that 71 percent of free samples were given to patients (Ref. 165). As an upper bound, assuming all samples are distributed to patients and that the uninsured receive them in proportion to their share of the population, approximately 300,000 MDIs (15 percent of 2 million) would reach the uninsured each year.

We expect coupons will do relatively little to improve access to albuterol among the uninsured. If 150,000 (5 percent (Ref. 154)) to 450,000 (15 percent) of the 3 million coupons reach uninsured patients each year and 100 percent of them are

[22] We found no information addressing how pharmaceutical companies distribute free samples among physicians and clinics, but assume that GSK will not

redeemed, this would increase albuterol MDI consumption by roughly 2,000-15,000 MDIs per year, based on the range of price elasticities considered.

Taking into account the offsetting effect of free samples and coupons, we focus on a range of 300,000 to 900,000 fewer albuterol MDIs sold each year as a result of increased prices stemming from removal of generic albuterol MDIs from the market. This assessment does not take into account Shering and GSK's patient assistance programs designed to provide free or low cost drugs to low-income patients as we are unable to assess how many albuterol MDI users are currently helped by these programs or how many more would be helped in the future. Over the course of the evaluation period, this would equal between 2.7 million and 8.1 million fewer albuterol MDIs sold. We recognize that due to varying measures of the size of the generic albuterol MDI market for the uninsured, uncertainty about the magnitude of price increases, consumers' response, and the impact of free samples and coupons, and other factors, the true impact of the rule could fall outside this range.

4. Effects on Medicare and Medicaid

In order to apportion the possible spending increases described above to the Medicaid and Medicare programs, FDA and

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systematically channel free samples away from low-income areas.

the Centers for Medicare & Medicaid Services (CMS) have analyzed utilization data related to Medicaid and Medicare, as well as Medicaid program spending data. As explained below, these data suggest that, were this rule in effect in 2003, Medicaid spending (including spending by States) would have increased by approximately $100 million for that year. In addition (based on 2001 utilization and 2004 prices), it would have increased drug spending on Medicare beneficiaries by ~~approximately $250~~ roughly $200 million, although this estimate includes copayments and coinsurance paid by individuals and may be too low because the estimate does not take into account increases in utilization associated with the increase in insurance coverage. These data yield the very rough estimate that the rule would increase Medicare and Medicaid spending by $3~~5~~00 million annually relative to a situation where access to generic albuterol CFC MDIs continued.

a. Medicaid. Medicaid spending on albuterol MDIs would have been higher by roughly $100 million in 2003--after taking into account rebates from drug companies--if albuterol CFC MDIs were not available. CMS estimates that 58 percent of this amount would be paid by the Federal Government and 42 percent by States.

Deriving this cost estimate required making some adjustments to available data. Our point of departure is the

State Drug Utilization Data, available at http://www.cms.hhs.gov/medicaid/drugs/drug5.asp for 2003. These data on utilization and spending on drugs paid for by the Medicaid program suggest that State reimbursements under Medicaid would have been approximately $127 million higher in 2003 if no albuterol CFC MDIs were available (that is, if only albuterol HFA MDIs were available). This estimate assumes substitutes for all albuterol CFC MDIs were purchased at the weighted average price of albuterol HFA MDIs. However, it does not take into account the effect of the rebates from drug companies to States and the Federal Government. CMS estimates that Medicaid program rebates constitute roughly 20 percent of gross spending on prescription drugs under the Medicaid program, suggesting that Medicaid spending on albuterol MDIs after rebates would have been roughly $100 million higher in 2003 if albuterol CFC MDIs were not available. It is important to note that this is a rough estimate, as rebates for a specific drug may differ from the 20 percent estimate. Incomplete data for 2004 suggest that comparable estimates for 2004 are higher but we believe that these are not reliable because of the incompleteness of the data.

b. Medicare. Our analysis of the impacts of this rule on Medicare addresses: (1) The total utilization of albuterol MDIs,

(2) the likely price increase, and (3) the aggregate spending increase.

CMS estimates that noninstitutionalized Medicare beneficiaries not eligible for Medicaid drug coverage filled about 8 million prescriptions for albuterol MDIs (including VENTOLIN and PROVENTIL) in 2001, based on the Medicare Current Beneficiary Survey (MCBS) and with an adjustment for under-reporting for aggregate analysis purposes. As noted below, this estimate is based on Medicare beneficiaries' self-reported outpatient prescription drug utilization, including prescriptions filled at both retail and mail order pharmacies. In addition, the adjustment for underreporting is normally used for aggregate use or spending data in MCBS and may not necessarily reflect actual underreporting for albuterol.

This analysis used data from the 2001 MCBS, a continuous, multipurpose survey of a nationally representative sample of Medicare beneficiaries. The survey is focused on health care use, cost, and sources of payment. No "paid claims" data on use of albuterol MDIs exist because Medicare will pay for albuterol MDIs only after the implementation of the new Medicare outpatient prescription drug benefit in January 2006. MCBS is the largest nationally representative set of data available on prescription drug utilization and spending by Medicare beneficiaries. The MCBS data have been used by both ~~the~~ CMS's

Office of the Actuary and the Congressional Budget Office to prepare estimates related to the new Medicare prescription drug benefit. However, because the data are self-reported, there are considerable limitations, most notably underreporting. CMS has studied the underreporting in the survey and has developed methods to adjust the data. For purposes of the estimates done for the Medicare drug benefit, the data on drug spending are analyzed in the aggregate (that is, for large collections of drugs). Estimates of individual drug product utilization and spending, however, may be even more vulnerable to the limitations inherent in self-reported utilization data.

A reliable assessment of impacts must avoid double counting of people who are eligible for both Medicaid and Medicare. With the implementation of the new Medicare prescription drug benefit, payment for outpatient prescription drugs on behalf of Medicare beneficiaries who are also eligible for prescription drug benefits under Medicaid will be moved from the Medicaid program to the Medicare program. For purposes of this analysis, this population of dually eligible beneficiaries (that is, Medicare beneficiaries also eligible for full-benefits under Medicaid) is excluded from the analysis of the MCBS data, since their albuterol MDI utilization is captured within the Medicaid data. Approximately half of total Medicaid prescription drug spending is for this dually eligible population. However, the

proportion will vary based on the type of drug involved. It is worth noting that albuterol MDIs are used to treat asthma in both the aged and disabled in the Medicare/Medicaid dually eligible population, as well as to treat asthma in children, who make up a large share of Medicaid beneficiaries.

For purposes of this analysis, we assess only data for the time periods for which data are available and we do not make projections for future years. As was noted in the impact analysis for the proposed rule on the Medicare prescription drug benefit (69 FR 46731, August 3, 2004), there is considerable uncertainty in making estimates when there is no program experience from prior years. This uncertainty is exacerbated in the context of making estimates related to a particular drug. For example, in the context of preparing aggregate estimates for the Medicare drug benefit, CMS makes assumptions about how increased coverage induces greater utilization and, based on the National Health Expenditures, projects growth in per capita drug spending. But making such calculations for a specific individual drug would be difficult and not likely reliable. Furthermore, in the case of albuterol MDIs, the drug is subject to large annual fluctuations in demand per user and size of population using the drug due to the nature of the conditions being treated, such as asthma where acute episodes may vary by environmental factors (for example, allergies), prevalence of

infectious diseases (for example, colds), and seasonal weather conditions (for example, temperature-related bronchial conditions). In addition, analyzing the effect on Medicare of a change related to one drug is further complicated, for example, by the need to consider the interactions with beneficiary cost-sharing in the context of the Medicare drug benefit design and the availability of additional low-income subsidies for certain populations. Also, the introduction of an albuterol HFA MDI from IVAX is expected to increase competition in the market to some extent, potentially dampening anticipated price increases in part. Our estimates, therefore, apply only to past years.

We believe that prices paid by private insurers offer a potentially reasonable approximation of prices negotiated in the context of a privately administered risk-based insurance program such as the new Medicare Part D drug plans. Using proprietary data from IMS Health, we determined that prices for patients with third-party insurance were on average ~~approximately $31~~ nearly $27 more per prescription for albuterol HFA MDIs than for albuterol CFC MDIs, according to IMS's National Prescription Audit for the first half of 2004 (~~analysis of IMS data~~Ref. 10). This price estimate reflects transactions in U.S. retail pharmacies, excluding Internet and mail order sales. It also reflects both payments by insurers and copayments or coinsurance payments by patients. We calculate the average price per

prescription for the albuterol HFA MDIs and the albuterol CFC MDIs, respectively, as the weighted average of the price per prescription of different firms' products, where the weights are the firms' shares of the total albuterol MDIs sold.

Given this estimate of the price difference that would have existed without CFC albuterol MDIs, spending by, and on behalf of, Medicare beneficiaries without Medicaid drug coverage could have been ~~approximately $250~~ roughly $200 million more in order to fill the 8 million prescriptions estimated to have been filled in 2001 (based on the MCBS data). This estimate is quite approximate because it relies on an estimate of albuterol MDI prescriptions from 2001 and estimates of prescription price differences from the first half of 2004. In addition, albuterol MDI use may grow as the Medicare drug benefit reduces the cost to individuals of using albuterol MDIs.

E. Alternative Phaseout Dates

In developing this rule, we considered removing the essential-use designation for ODSs in albuterol MDIs for different dates between 12 months after issuance of a final rule and December 31, 2009. As shown previously, earlier removal would increase consumer expenditures while increasing environmental benefits. A later date would reduce the potential health effect from reduced access, but also reduce the

environmental benefit and potentially put at risk international cooperation. We also considered and rejected small business exemptions as inconsistent with international commitments.

Table ~~3~~4 shows the effects of selecting December 31, 2005, as the effective date, and T~~t~~able ~~4~~5 shows the effects if we had selected December 31, 2009 (assuming continued availability of CFCs).

Table ~~3~~ 4.--Effects of Phaseout as of December 31, 2005

Number of Affected of Albuterol MDIs (million)	Increased Expenditures for Albuterol MDIs Present Value in 2005 (billions)		Possible Reduction in MDI Use (millions)	Reduced Aggregate CFC Emissions Related to Phaseout (metric tons)	Relative Return on Investment to New Technology (return for 12/31/08 phaseout = 1)	
	3-percent discount rate	7-percent discount rate			3-percent discount rate of	7-percent discount rate of
576	$11.6	$9.3	3.6 to 9.8	14,400	1.4	1.5

Table ~~4~~ 5.--Effects of Phaseout as of December 31, 2009

Number of Affected Albuterol MDIs (million)	Increased Expenditures for Albuterol MDIs Present Value in 2005 (billions)		Possible Reduction in Albuterol MDI Use (millions)	Reduced Aggregate CFC Emissions Related to Phaseout (metric tons)	Relative Return on Investment to New Technology (return for 12/31/08 phaseout = 1)	
	3-percent discount rate	7-percent discount rate			3-percent discount rate	7-percent discount rate
384	$7.3	$5.3	2.4 to 7.2	8,400	.88	.85

F. Sensitivity Analyses

We have conducted some sensitivity analyses to address how key sources of uncertainty may affect our estimates. Our key focus is the effect of alternative dates for when generic competition for albuterol HFA MDIs may begin. As a result, we present the effects of a December 31, 2008, phaseout date in Table 6, assuming that generic albuterol HFA MDIs arrive in 2010. In Table 7, we present similar effects assuming that generic competition arrives in 2015.

Table ~~5~~6.--Effects of Phaseout on December 31, 2008--Assuming Generic Entry in 2010

Number of Affected Albuterol MDIs (millions)	Increased Expenditures for Albuterol MDIs Present Value in 2005 (billions)		Possible Reduction in MDI Use (millions)	Reduced Aggregate Emissions Related to Phaseout (metric tons)	Relative Return on Investment to New Technology (return for 12/31/08 phaseout with generic entry in 2017 = 1)	
	3-percent discount rate	7-percent discount rate			3-percent discount rate	7-percent discount rate of
96	$2.1	$1.7	0.6 to 1.8	2,400	.25	.27

Table ~~6~~7.--Effects of Phaseout on December 31, 2008--Assuming Generic Entry in 2015

Number of Affected Albuterol MDIs (millions)	Increased Expenditures for Albuterol Present Value in 2005 (billions)		Possible Reduction in MDI Use (millions)	Reduced Aggregate Emissions Related to Phaseout (metric tons)	Relative Return on Investment to New Technology (return for 12/31/08 phaseout with genetic entry in 2017 = 1)	
	3-percent discount rate	7-percent discount rate			3-percent discount rate	7-percent discount rate
336	$6.7	$5.2	2.1 to 5.6	8,400	.81	.84

These sensitivity analyses show that the eventual date that generic competition arrives will have a substantial effect on the total reduction in albuterol MDI use and the aggregate reductions in CFC emissions. Further analysis of the arrival of generic competition would require an evaluation of the legal merits of the different patents, but such an evaluation is beyond the expertise of FDA.

G. Small Business Impact

Current ~~D~~HHS guidance (Ref. 17~~6~~) suggests that a 3 to 5 percent impact on total costs or revenues of small entities could constitute a significant regulatory impact. We lack the data to certify that this final rule will not have a significant economic impact on a substantial number of small entities. Therefore, this analysis, together with other relevant sections of this document, serves as FDA's Regulatory Flexibility Analysis, as required under the Regulatory Flexibility Act.

1. Affected Sector and Nature of Impacts

The affected industry sector includes manufacturers of pharmaceutical products (NAICS 32514). We obtained data on this industry from the 1997 Economic Census and estimated revenues per establishment. Although other economic measures, such as profitability, may provide preferable alternatives to revenues as a basis for estimating the significance of regulatory

impacts, we do not believe it would change the results of this analysis.

The impact of this rule on generic manufacturers is the lost revenues currently generated by sales of generic albuterol CFC MDIs. While "lost revenues" are an imperfect measure, because production resources could be shifted to alternative markets, they provide a measure that suggests the magnitude of the impact.

The Small Business Administration (SBA) has defined as small any entity in this industry with fewer than 750 employees. According to Census data, 84 percent of the industry is considered small. The average annual revenue for a small entity is $26.6 million per entity. However, the agency does not have revenue information specific to the affected entities. According to retail sales in the first half of 2004, of the 22.7 million generic or relabeled annual prescriptions for albuterol, approximately 63 percent (14.3 million MDIs) were distributed by Schering, a large firm, under the Warrick label. Six different companies marketed the other 8.4 million albuterol MDIs, with three companies accounting for over 99 percent of these 8.4 million (~~analysis of IMS data~~Ref. 10). According to data collected by the Congressional Budget Office (Ref. 1~~8~~7), the value of shipments from manufacturers of generic drug products

accounts for approximately 35 percent of the retail price of the product. If so, revenue from 1.7 million albuterol MDIs would approximate $8.0 million per year (1.7 million prescriptions X $13.50 per generic prescription X 35 percent). Because we lack company-specific revenue data, we are unable to estimate the impact of this rule on these small entities. To the extent that generic albuterol HFA MDIs might become available prior to the removal of the essential-use designation, any impact on small entities would be mitigated.

2. Outreach

The Montreal Protocol and Clean Air Act have been in place for more than a decade. Manufacturers of albuterol CFC MDIs have long known that CFCs would eventually lose their essential-use designations for this purpose. During the proposal stage of this rule-making, we specifically solicited comments on the impact on small entities. No comments were received that explicitly addressed this issue.

H. Conclusion

This final rule could result in increased health care expenditures of more than $1.1 billion for each year between the removal of the essential-use designation and reintroduction of generic competition at patent expiration. Taking into account GSK's commitment to provide free samples and coupons, we

estimate that higher prices due to the elimination of generic competition will reduce the number of MDIs sold by between 300,000 and 900,000 per year. This estimate does not take into account Shering and GSK's patient assistance programs designed to provide free or low cost drugs to low-income patients as we are unable to assess how many albuterol MDI users are currently helped by these programs or how many more would be helped in the future. In addition, each year without using CFCs in albuterol MDIs will reduce atmospheric emissions of ODSs by 1,200 metric tons and provide increased investment returns for environmentally friendly technology that may induce further gains. Removal of the essential-use designation is consistent with FDA's role in determining the essentiality of MDIs under section 601 of the Clean Air Act, and also meets U.S. obligations under international agreements. Finally, we lack the data to certify that this final rule will not have a significant economic impact on a substantial number of small entities.

VI. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. U.S. Food and Drug Administration, "Guidance for Industry: Integration of Dose-Counting Mechanisms into MDI Drug Products," March 2003.

2. Penick, Brock T. et al., "Accuracy of Float Testing for Metered-Dose Inhaler Canisters," Journal of the American Pharmaceutical Association, 42:582, July/August 2002.

3. Craig-McFeely, P.M. et al., "Prospective Observational Cohort Safety Study to Monitor the Introduction of a Non-CFC Formulation of Salbutamol with HFA 134a in England," International Journal of Clinical Pharmacology and Therapeutics, 41:67-76, 2003.

4. Goldman, J. et al., "Pharmacy Benefits and the Use of Drugs by the Chronically Ill," The Journal of the America Medical Association, May 19, 2004; 291:2344-2350, 2349.

5. United Nations Environmental Programme, "Production and Consumption of

Ozone-Depleting Substances 1986-2000," 2003.

6. The Benefits and Costs of the Clean Air Act: 1990-2010, (http://www.epa.gov/air/sect812/copy.html)

7. Mannino, D.M. et al., "Chronic Obstructive Pulmonary Disease Surveillance--United States, 1971-2000," Morbidity and Mortality Weekly Report, 51(SS06):1-16, August 2, 2002.

8. American Lung Association, "Trends in Asthma Morbidity and Mortality," Epidemiology & Statistics Unit, Research and Scientific Affairs, Table 7, April 2004.

9. Mannino, D.M. et al., "Surveillance for Asthma--United States, 1980-1999," Morbidity and Mortality Weekly Report, 51(SS01):1-13, March 29, 2002.

10. Analysis completed by FDA based on information provided by IMS Health, IMS National Prescription Audit™, 2004; IMS Health, IMS MIDAS™, Q1/2004--Q2/2004. These data can be purchased from IMS Health. Please send all inquiries to: IMS Health, Attn:

Brian Palumbo, Account Manage, 660 W. Germantown Pike, Plymouth Meeting, PA 19462.

11~~0~~. Rozek, R.P., and E.R. Bishko, "Economics Issues Raised in the FDA's Proposed Rule on Removing the Essential-Use Designation for Albuterol MDIs," National Economic Research Associates, August 13, 2004 (FDA Docket No. 2003P-0029/C25).

12~~1~~. Agency for Healthcare Research and Quality, "Albuterol Inhalers: Prescriptions per User, Price per Prescription and Expenditure Given Use," spreadsheet prepared at FDA's request for this rulemaking, 2004.

13~~2~~. Ringel, J.S. et al., "The Elasticity of Demand for Health Care," National Defense Research Institute, Rand Health, 2002.

14~~3~~. U.S. Census Bureau, "Income, Poverty, and Health Insurance Coverage in the United States: 2003," Current Population Reports, U.S. Department of Commerce, August 2004, pp. 14-15.

154. Morelli, D., and M.R. Koenigsberg, "Sample Medication Dispensing in a Residency Practice," Journal of Family Practice, 34(1):42-48, 1992.

165. Peterson, M.C. et al., "Disposition of Pharmaceutical Samples from a Private Medical Clinic," Journal of the American Pharmacists Association, 44(3):397-398, 2004.

176. U.S. Department of Health & Human Services, "Guidance on Proper Consideration of Small Entities in Rulemakings of the U.S. Department of Health and Human Services," May 2003.

187. Congressional Budget Office, "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," July 1998.

VII. The Paperwork Reduction Act of 1995

This final rule contains no collections of information. Therefore, clearance by OMB under Paperwork Reduction Act of 1995 is not required.

VIII. Federalism

We have analyzed this final rule in accordance with the principles set forth in Executive Order 13132. We have determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. While this rule may result in States increasing spending for albuterol MDIs in programs such as Medicaid, the increased spending is not a substantial direct compliance cost, as the term is used in Executive Order 13132. Accordingly, we have concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

List of Subjects in 21 CFR Part 2

Administrative practice and procedure, Cosmetics, Devices, Drugs, Foods.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Clean Air Act and under authority delegated to the Commissioner of Food and Drugs, after consultation with the Administrator of the Environmental Protection Agency, 21 CFR part 2 is amended as follows:

PART 2--GENERAL ADMINISTRATIVE RULINGS AND DECISIONS

1. The authority citation for 21 CFR part 2 continues to read as follows:

Authority: 15 U.S.C. 402, 409; 21 U.S.C. 321, 331, 335, 342, 343, 346a, 348, 351, 352, 355, 360b, 361, 362, 371, 372, 374; 42 U.S.C. 7671 et seq.

§2.125 [Amended]

2. Section 2.125 Use of ozone-depleting substances in foods, drugs, devices, or cosmetics is amended by removing and reserving paragraph (e)(2)(i).